REMARKS

Claims 1-2 are currently pending. No amendment is made to claims 1-2.

All prior obviousness rejections have been withdrawn.

Claims 1 and 2 are rejected under 35 U.S.C. § 103(a) as being obvious over Meheus et al. [Postgraduate Med. J. 63(Supp 2):139-141, 1987 (IDS); "Meheus"] in view of Whalen et al. (Ann. N.Y. Acad. Sci. 772:64-76, 1995; "Whalen") and Schirmbeck et al. (J. Virol. 69(10): 5929-34, 1995; "Schirmbeck"). According to the Examiner, Meheus teaches vaccination of human neonates with a protein vaccine, but not "a naked recombinant nucleic acid encoding a relevant epitope to the target HBsAg epitopes;" Whalen teaches that "DNA-mediated immunization with the HBsAg-expressing plasmid vectors induces strong CTL responses as well as a dominant Th1 phenotype among the splenic lymphocytes of immunized mice;" and Schirmbeck teaches that immune responses were observed in mice immunized by intramuscular transfer of plasmid DNA encoding HBsAg epitopes. The Examiner contends that "it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to apply plasmid DNA hepatitis B virus surface antigen (HBsAg) vaccine in neonates at birth or 1 month . . . with a reasonable expectation of success." Applicants respectfully traverse this rejection.

The pending claims relate to a method for immunizing an infant human against a target antigen or inducing a cytotoxic T cell response against a pathogen in an infant human, comprising inoculating the infant human with a naked recombinant nucleic acid encoding a relevant epitope of the target antigen or a target antigen associated with the pathogen within the age of birth to one month. As disclosed in the specification, "[t]he concept of tolerance is associated with the traditional belief that neonates are themselves incapable of mounting an effective immune response," and "[i]t has been generally believed that neonates rely on maternal antibodies (passively transferred via the placenta) for immunity, until the neonate begins to synthesize its own IgG anti-bodies (at about 3-4 months after birth, in humans)" (page 3, lines 1-5 (citation omitted)). The cited references fail to teach or suggest the claimed invention.

1. Meheus does not teach inoculation with a naked nucleic acid

As conceded by the Examiner, Meheus does not teach a method comprising inoculating an infant human with a naked nucleic acid encoding an epitope within the age of birth to one month.

In Meheus, infants born to HBsAg-positive mothers (Group I) and infants born to women without HBV markers (Group II) were vaccinated with a protein vaccine within 24 hours after birth according to a 0, 1, and 2 month schedule, with a booster dose planned 12 months later, and the immunogenicity of the vaccine was evaluated based on the seroconversion rates measured in sera collected from the newborns (abstract). The seroconversion rate for Group I increased from 40% at Month 1 to 86% at Month 4 (Table I) while the seroconversion rate for Group II increased from 46% at Month 1 to 100% at Month 4 (Table II). The experimental design and results reported in Meheus are consistent with the then conventional view of infant tolerance and the general knowledge that human neonates start to synthesize their own antibodies at about 3-4 months after birth.

Meheus does not teach whether and/or to what extent an epitope encoded by a nucleic acid would be expressed and capable of inducing immune responses in an infant human after being inoculated with the naked nucleic acid within the age of birth to one month. One of ordinary skill in the art would have expected a lower amount of the expressed epitope and, therefore, a lower seroconversion rate in an infant human inoculated with a naked nucleic acid encoding the epitope than an infant human inoculated with the epitope. Thus, one of ordinary skill in the art would not have been motivated to modify the protein vaccination method disclosed in Meheus by inoculating an infant human with a naked nucleic acid within the age of birth to one month with a reasonable expectation of success in inducing immune responses in the infant human.

2. Whalen and Schirmbeck do not teach inoculation of an infant human within the age of birth to one month or a non-human infant of an equivalent age

Neither Whalen nor Schirmbeck teaches a method comprising inoculating an infant human with a naked nucleic acid within the age of birth to one month or a non-human infant of an equivalent age.

Whalen is cited for teaching "the use of plasmid vectors expressing the HBsAg, along with improved protocols for transfection of muscle fibers and methods with which to investigate the characteristics of the strong immune response given by this antigen after DNA-mediated immunization." In particular, Whalen teaches intramuscular injection of plasmids in mice at page 68 citing Reference 4 (Davis et al., Vaccine 12:1503-9, 1994; "Davis 1994;" attached as Ex. A), Reference 5 (Davis et al., Hum. Mol. Genet. 1993, 2(11):1847-51; "Davis 1993;"

attached as Ex. B), and Reference 6 (Michel et al., Proc. Natl. Acad. Sci. USA, 1995, 92:5307-11; "Michel;" attached as Ex. C). Davis 1994 and Davis 1993 teach *in vivo* gene transfer to mice of approximately 6-7 weeks old (Davis 1994, p. 1505; Davis 1993, p.1851) while Michel teaches *in vivo* gene transfer to 6- to 8-week-old mice (Michel, p. 5308).

Schirmbeck is cited to "supplement[] the teachings of Whalen by teaching mice immunized either by injection of a low dose of recombinant HBsAg protein preparations, by infection with recombinant vaccinia virus carrying an HBsAg-encoding gene, or by intramuscular transfer of plasmid DNA encoding HBsAg epitopes...." In particular, Schirmbeck teaches inoculating mice at 12 to 16 weeks of age (p. 5930).

While a human infant ranges from birth to about nine months, a mouse infant ranges from birth to about four weeks of age (specification, page 13, line 30 to page 14, line 1). Thus, Whalen, Davis 1994, Davis 1993, Michel and Schirmbeck teach inoculating adult mice, not mice of an age equivalent to an infant human within the age of birth to one month. Accordingly, Whalen and Schirmbeck do not teach or suggest inoculating a human infant at an age ranging from birth to one month for immunization or for inducing a cytotoxic T cell response, and one of ordinary skill in the art would not have been motivated by Whalen and Schirmbeck to apply the plasmid DNA HBsAg epitope vaccine of Schirmbeck in neonates of Meheus, or to inoculate an infant human with a naked nucleic acid encoding HBsAg within the age of birth to one month with a reasonable expectation of success in immunizing or inducing cytotoxic T cell response against HBsAg in the infant human.

3. Combination of Meheus, Whalen and Schirmbeck

A combination of Meheus, Whalen and Schirmbeck does not teach each and every element of claim 1 or 2. These references do not teach or suggest inoculating an infant human with a naked nucleic acid within the age of birth to one month. It was unpredictable whether and/or to what extent an epitope encoded by a nucleic acid would be expressed and capable of immunizing or inducing a cytotoxic T cell response in an infant human inoculated with the naked nucleic acid within the age of birth to one month.

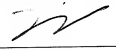
For the foregoing reasons, one skilled in the art would not have been motivated to combine Meheus, Whalen and Schirmbeck with a reasonable expectation of success in achieving the claimed invention of claim 1 or 2. Thus, the Examiner has not established a *prima facie* case of obviousness. Applicants respectfully request withdrawal of this obviousness rejection.

CONCLUSION

Entry of the foregoing remarks into the file of the above-identified application is respectfully requested. Withdrawal of the sole rejection is also requested.

The Commissioner is hereby authorized to charge payment of any additional fees associated with this communication or refund any overpayments to Deposit Account No. 02-4377.

Respectfully submitted,



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